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Renal Cell Carcinoma Renal cell carcinomas account for 90–95% of malignant neoplasms arising from the kidney. Notable features include frequent diagnosis without symptoms, resistance to cytotoxic agents, robust activity of angiogenesis-targeted agents, immune infiltration commonly rendering tumors susceptible to checkpoint-directed immunotherapy, and a variable clinical course for patients with metastatic disease, including anecdotal reports of spontaneous regression. Most of the remaining

TABLE 90-1	Hereditary Renal Cell Tumors	SYNDROME	CHROMOSOME(S)	GENE	PROTEIN	KIDNEY TUMOR TYPE	ADDITIONAL CLINICAL FINDINGS
von Hippel-Lindau syndrome	3p25	VHL	von Hippel-Lindau protein	Clear cell	Hemangioblastoma of the retina and central nervous system; pheochromocytoma; pancreatic and renal cysts; neuroendocrine tumors		
Hereditary papillary RCC	7p31	MET	MET	Papillary	Bilateral and multifocal kidney tumors		
Hereditary leiomyomatosis and RCC (HLRCC syndrome)	1q42	FH	Fumarate hydratase	FH-deficient/HLRCC	syndrome– associated RCC		
Birt-Hogg-Dubé syndrome	17p11	FLCN	Folliculin	Chromophobe; clear cell; oncocytoma			
Tuberous sclerosis	9q34 16p13	TSC1 TSC2	Hamartin Tuberin	BAP1 tumor predisposition syndrome			
3p21	BAP1	BAP1	Mostly clear cell, but chromophobe and papillary have also been reported				

Abbreviations: ESC, eosinophilic solid and cystic; FH, fumarate hydratase; HLRCC; hereditary leiomyomatosis and RCC; RCC, renal cell carcinoma; TSC, tuberous sclerosis.

5–10% of malignant neoplasms arising from the kidney are transitional cell carcinomas (urothelial carcinomas) originating in the lining of the renal pelvis. See Chap. 91 for transitional cell carcinomas.

■ ■ **EPIDEMIOLOGY** The incidence of cancers of the kidney and renal pelvis rose for three decades, reached a plateau of approximately 64,000 cases annually in the United States between 2012 and 2018, but has since increased to approximately 81,000 cases annually, resulting in close to 15,000 deaths per year. It is the seventh most common cancer overall in the United States, the sixth most common in males, and the ninth most common in females; the male-to-female ratio is 2:1.

Although this malignancy may be diagnosed at any age, it is uncommon in those under 45 years, and incidence peaks between the ages of 55 and 75 years. Many factors have been investigated as possible contributing causes; associations include cigarette smoking, obesity, and hypertension. Risk is also increased for patients with polycystic kidney disease that has been complicated by chronic renal failure. Most cases of renal cell carcinoma (RCC) are sporadic, although familial forms have been reported (Table 90-1). One well-established example includes clear cell RCC arising in the context of von Hippel-Lindau (VHL) syndrome, an autosomal dominant disorder. Genetic studies identified the VHL gene on the short arm of chromosome 3. Individuals with VHL syndrome have a 70% estimated lifetime risk of developing clear cell RCC. Other VHL-associated neoplasms include retinal hemangioma, hemangioblastoma of the spinal cord and cerebellum, pheochromocytoma, and neuroendocrine tumors. Belzutifan, an oral inhibitor of hypoxia-inducible factor (HIF-2 α), is approved for treatment of VHL-associated cancers. Birt-Hogg-Dubé syndrome is a rare human autosomal dominant genetic disorder characterized by fibrofolliculomas (benign tumors arising in hair follicles), pulmonary cysts, and RCCs of varying histologies, most commonly the chromophobe type, occurring in about a third of patients. This disorder is associated with mutations in the FLCN gene, which codes for folliculin. Other hereditary syndromes are summarized in Table 90-1.

CHAPTER 90 Renal Cell Carcinoma ■ ■ **PATHOLOGY AND GENETICS** Renal cell malignancies represent a heterogeneous group of tumors with distinct histopathologic, genetic, and clinical features (Table 90-2). Categories include clear cell carcinoma (70% of cases), papillary RCC (10–15%), chromophobe RCC ($\leq$ 5%), molecularly defined entities such as TFE3-rearranged RCC (<5%), and other less common variants. Papillary tumors can be bilateral and multifocal. Chromophobe tumors tend to have a more indolent clinical course. TFE3-rearranged RCC, rare in adult patients, is the predominant histology in children. SMARCB1-deficient RCC, previously called renal medullary leiomyoma; uterine leiomyoma/ leiomyosarcoma; facial fibrofolliculoma; pulmonary cysts; angiomyolipomas; TSC-associated lymphangioleiomyomatosis; rare RCC with variety of histologic appearances including eosinophilic solid and cystic (ESC) RCC; angiofibroma, subungual fibroma; cardiac rhabdomyoma; adenomatous small intestine polyps; pulmonary and renal cysts; cortical tuber; subependymal giant cell astrocytomas; atypical Spitz tumors; uveal melanoma; cutaneous melanoma; basal cell carcinoma; malignant mesothelioma

TABLE 90-2 Classification of Malignant Epithelial Neoplasms Arising from the Kidney

CARCINOMA TYPE	CHARACTERISTIC GROWTH PATTERN	CHROMOSOMAL EVENTS
Clear cell	Varying growth patterns, including acinar, solid and sarcomatoid	Papillary: Papillary or sarcomatoid +7, +17, 9p-MET, CDKN2A (focal deletions) Chromophobe: Solid, tubular, or sarcomatoid Whole arm losses (1, 2, 6, 10, 13, 17,

and 21) TFE3-rearranged and TFEB-altered renal cell carcinomas Mimicking clear cell and papillary variants Xp11.2 translocations; t(6;11) translocations SMARCB1-deficient renal medullary carcinoma Varying growth patterns, including cribriform, reticular, sarcomatoid, adenoid, and microcystic carcinoma, is rare, very aggressive, and associated with sickle cell trait. Tumors that do not meet criteria for defined variants are generally referred to as “unclassified” with variable clinical courses. Clear cell tumors, the predominant histology, are found in >80% of patients who develop metastases and arise from the epithelial cells of the proximal tubules. Loss of chromosome 3p is uniformly seen as the earliest event in the development of these cancers. This leads to loss of heterozygosity for a number of relevant 3p genes, including VHL, PBRM1, BAP1, and SETD2, which can be functionally silenced through secondary events in the remaining allele. VHL encodes a tumor-suppressor protein that is involved in regulating the transcription of vascular endothelial growth factor (VEGF) and a number of other effectors through ubiquitination of hypoxia-inducible factors (HIF). Inactivation of VHL, through upregulation of VEGF signaling, promotes tumor angiogenesis and growth, ultimately rendering clear cell RCC cells susceptible to antiangiogenesis therapy. PART 4 Oncology and Hematology Large-scale sequencing efforts have helped elucidate recurrent patterns of genomic evolution that correlate with distinct clinical phenotypes, e.g., varying levels of aggressiveness or specific patterns of metastatic spread. For example, early loss of chromosome 9p appears to confer a high risk for early metastatic dissemination and correlates with poor cancer-specific survival. A growing number of other RCC variants are well defined (see Table 90-2 for examples) yet can further vary by molecular features. For instance, up to 15% of RCCs are of the papillary subtype, and variant features can be distinguished by light microscopy but also molecular assays. Activating mutations in the MET oncogene or gain of chromosome 7 (where MET is located) are hallmark events of certain papillary variants and considered actionable via targeted MET inhibitors. Tumors of the less common chromophobe subtype originate from the distal nephron. They are typically characterized by aneuploidy with common loss of an entire chromosome copy for chromosomes 1, 2, 6, 10, 13, and 17. ■ ■CLINICAL PRESENTATION

Presenting signs and symptoms may include hematuria, flank or abdominal pain, and a palpable mass. Other symptoms are fever, weight loss, anemia, and a varicocele. Tumors are, however, commonly detected as an incidental finding on a radiograph. Widespread use of radiologic cross-sectional imaging (computed tomography [CT], magnetic resonance imaging [MRI]) contributes to earlier detection of renal masses during evaluation for other medical conditions. The increasing number of incidentally discovered low-stage tumors has contributed to an improved 5-year survival for patients with RCC and increased use of nephron-sparing surgery (partial nephrectomy). A spectrum of paraneoplastic syndromes has been associated with these malignancies, including erythrocytosis, hypercalcemia, nonmetastatic hepatic dysfunction (Stauffer’s syndrome), and acquired dysfibrinogenemia. Erythrocytosis is noted at presentation in only about 3% of patients. Anemia, commonly a sign of more advanced disease, is more common. Kidney cancer was called the “internist’s tumor” since it was often discovered from the initial presentation of a paraneoplastic

GENES WITH RECURRENT SOMATIC ALTERATIONS 3p-, 5q+, 14q-, 9p- VHL, PBRM1, BAP1, SETD2 TP53, PTEN, TERT promotor TFE3 gene fusions, TFEB gene fusions +8q, 22q-, 22q translocations SMARCB1 (focal deletions, mutations, gene fusions), SETD2 syndrome. This was more common before the era of modern imaging, as was initial presentation by the classic triad of hematuria, flank pain, and a palpable abdominal mass. The standard evaluation of patients with suspected renal tumors includes a CT scan of the abdomen and pelvis, chest radiograph, and urine analysis. If

metastatic disease is suspected from the chest radio graph, a CT of the chest is warranted. MRI is useful in evaluating the inferior vena cava in cases of suspected tumor involvement or invasion by thrombus, or when intravenous contrast administration given with CT is prohibited by impaired renal function. In clinical practice, any solid renal masses should be considered malignant until proven otherwise; a definitive diagnosis is required. If no metastases are demonstrated, surgery is indicated, even if the renal vein or inferior vena cava is invaded. In small tumors (particularly those of clear cell variant), the risk of impending metastatic spread is lower and surgery can potentially be delayed. In that setting, a needle biopsy should be performed to confirm the underlying histology, and radiographic surveillance is indicated until the time of surgery. The differential diagnosis of a renal mass includes cysts, benign neoplasms (adenoma, angiomyolipoma, oncocytoma), inflammatory lesions (pyelonephritis or abscesses), and other malignancies originating in the kidney such as transitional cell carcinoma of the renal pelvis, sarcoma, lymphoma, and Wilms' tumor or metastases from cancers originating in other organs. All of these are less common causes of renal masses than is RCC. The most common sites of distant metastases are the lungs, lymph nodes, liver, bone, and brain. These tumors may follow an unpredictable and protracted clinical course. ■ ■

STAGING AND PROGNOSIS Staging is based on the American Joint Committee on Cancer (AJCC) staging system (Fig. 90-1). Stage I tumors are ≤ 7 cm in greatest diameter and confined to the kidney; stage II tumors are >7 cm and confined to the kidney; stage III tumors extend through the renal capsule but are confined to Gerota's fascia, grossly infiltrate the renal vein, or involve regional lymph nodes (N1); and stage IV disease includes tumors that have invaded adjacent organs or involve nonregional lymph nodes or distant metastases. Sixty-five percent of patients present with stage I or II disease, 15–20% with stage III, and 15–20% with stage IV. The 5-year survival rate is currently 77% across all RCCs but varies greatly by stage. Prognostic risk models are helpful for counseling patients diagnosed with metastatic disease and for anticipating survival rates when designing a clinical trial. A widely used prognostic model for advanced disease, the International Metastatic RCC Database Consortium (IMDC) risk model, incorporates six factors shown to correlate with worse survival: poor performance status, low hemoglobin concentration, high serum calcium, high neutrophil levels, high platelet levels, and <1 -year interval from diagnosis to systemic treatment. Patients with zero risk factors achieve significantly longer median survival (≥ 5 years) than patients with one or two risk factors (~ 4 years) and those with three to six risk factors (~ 3 years) when treated with first-line checkpoint inhibitor-containing combination regimens (see below).

T1 T2 Involvement TNM TX Primary not involved T1 T1a T1b ≤ 7 cm ≤ 4 cm

“ 4 cm T2 T2a T2b 7 cm to ≤ 10 cm 7 cm 10 cm T3 into major veins or perinephric tissues T3a in renal vein, renal sinus fat, or pelvicalyceal system T3b T3c into vena cava into vena cava T3 T4 T4 invasion beyond Gerota's fascia Regional NX Regional lymph nodes not assessed N0 No regional lymph node involvement N1 Regional lymph node involvement Distant Metastases M0 M1 No distant metastases Distant metastases, including nonregional lymph nodes FIGURE 90-1 Renal cell carcinoma staging. TNM, tumor-node-metastasis. TREATMENT Renal Cell Carcinoma LOCALIZED TUMOR The standard management for stage I or II tumors and selected cases of stage III disease is radical or partial nephrectomy.

A radical nephrectomy involves en bloc removal of Gerota's fascia and its contents, including the kidney, and commonly the ipsilateral adrenal gland and regional lymph nodes that appear abnormal on imaging or intraoperatively. Open, laparoscopic, or robotic surgical techniques may be used. The role of a template lymphadenectomy in patients without apparent lymphadenopathy is controversial. Extension into the renal vein or inferior vena cava (stage III disease) does not preclude resection, which would then include thrombectomy. Nephron-sparing approaches, i.e., open or laparoscopic partial nephrectomy, may be appropriate depending on the size and location of the tumor. This approach is particularly relevant for patients with solitary kidneys, bilateral tumors, or chronic renal insufficiency but can also be applied electively to resect small masses for patients with normal kidney function. Radical nephrectomy carries a greater risk for chronic kidney disease and cardiovascular morbidity and mortality. Adjuvant systemic therapies, including cytokines and targeted agents, have been studied in randomized clinical trials, largely with negative results. The checkpoint inhibitor pembrolizumab is approved in patients with increased risk of recurrence following nephrectomy, where 12 months of therapy was shown to improve disease-free survival compared to placebo. For those with low risk of recurrence, the standard of care remains active surveillance after nephrectomy. METASTATIC DISEASE Surgery has a limited role for patients with metastatic disease. Long-term survival may occur in patients who relapse with a solitary site that is removed (metastasectomy). Nephrectomy despite presence of metastases (cytoreductive nephrectomy) is considered for carefully selected patients with stage IV disease. One indication for this approach can be to alleviate pain or hemorrhage of a primary tumor. Radiation therapy is used for palliation of bone or brain metastases. The type of radiotherapy most commonly used is external beam therapy, including stereotactic radiosurgery and other forms of image-guided radiotherapy.

Extent of Disease Anatomic Stage/Prognostic Groups I N0 M0 T1 II N0 M0 T2 III N0 or N1 N1 M0 M0 T3 T1 or T2, limited to kidney IV Any N Any N M0 M1 T4 Any T limited to kidney not beyond Gerota's fascia not beyond Gerota's fascia below diaphragm above diaphragm including contiguous extensions & into ipsilateral adrenal gland CHAPTER 90 Systemic therapy is the mainstay of care for metastatic disease. The timing of initiating such treatment should be carefully considered; some patients are asymptomatic at diagnosis, and with indolent behavior, it may be best to document progression before initiating treatment. Renal Cell Carcinoma Metastatic RCC is refractory to cytotoxic chemotherapy. Patients are treated with molecularly targeted agents, including targeted immunotherapies, i.e., checkpoint inhibitors. Treatments are continued with noncurative intent while tolerated and until disease progression is evident on cross-sectional imaging. Outcomes for patients with metastatic disease improved when increased understanding of underlying biology led to the successful development of several tyrosine kinase inhibitors (TKIs) targeting proangiogenic signaling through the VEGF receptors as well as allosteric inhibitors of mammalian target of rapamycin (mTOR) signaling. Serial large-scale randomized trials demonstrated that such agents, typically orally available, could be administered sequentially and

in combination. Pivotal studies, by design, defined a dedicated space for each regimen in treatment-naïve or pretreated patients

(Table 90-3). Targeted immunotherapies were introduced after VEGF- and mTOR-directed agents had established standards of care in the first- and second-line setting. Nivolumab, a checkpoint inhibitor targeting PD-1, demonstrated superior overall survival compared to the mTOR inhibitor everolimus in a randomized trial in patients who had progressed on prior TKI therapy, challenging the standard approach in pretreated patients and positioning nivolumab as the new second-line agent of choice. Subsequently, immunotherapy combination regimens demonstrated efficacy in randomized trials conducted in treatment-naïve patients. In separate studies, four doublets demonstrated survival benefit over standard sunitinib therapy and changed the standard of care for untreated metastatic clear cell RCC toward two-drug, immunotherapy-containing regimens: nivolumab in combination with the CTLA-4-directed check point inhibitor ipilimumab; the TKI axitinib together with the PD-1 inhibitor pembrolizumab; the TKI cabozantinib plus nivolumab; and the TKI lenvatinib paired with pembrolizumab. These combinations demonstrated objective radiographic responses in 40–70% of patients, and complete radiographic disappearance of cancer is achieved in about 10% of patients. The majority of such anticancer effects were reported to be long-lasting. With an ever-growing number of approved options directed toward different molecular targets, biomarkers are urgently needed to help individualize therapeutic choices and to gain insight as to

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